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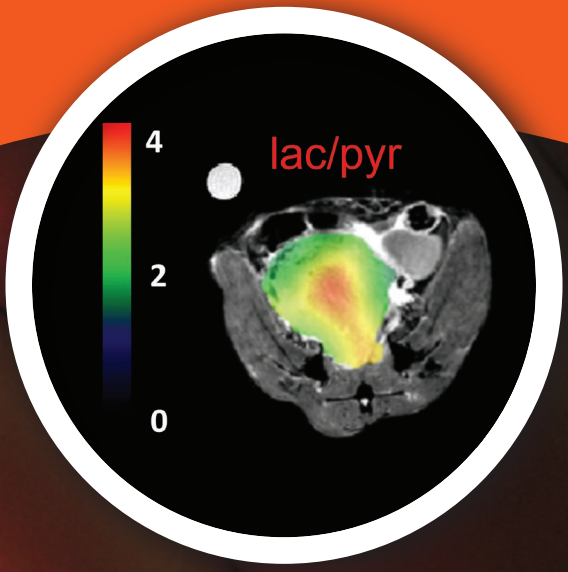
RESEARCH PRODUCTS

Hyperpolarized Substrates

Sensitivity Enhancement Using Hyperpolarization



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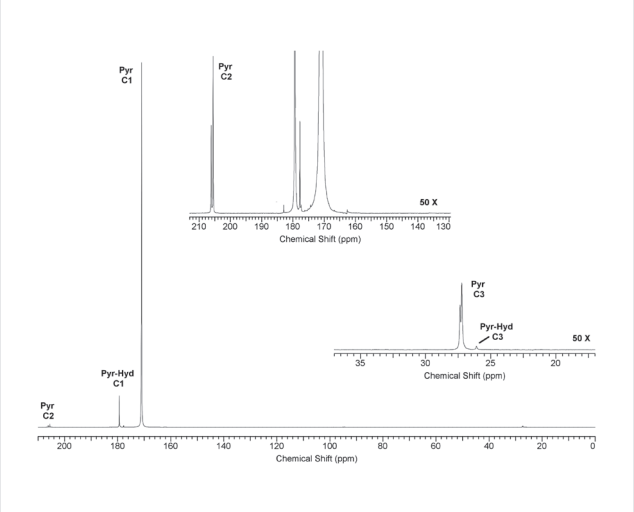
It not surprising that many developments in the field of magnetic resonance are aimed to improve sensitivity. One can blame NMR spectroscopy's inherently poor sensitivity on the very small population differences between magnetically induced nuclear spin states. The extent of these population differences (also referred to as the degree of polarization) is normally dictated by the Boltzmann distribution and is dependent on magnetic field strength, temperature and the gyromagnetic ratio of the observed nucleus. Methods have emerged and recently refined that transfer nuclear polarization from a highly polarized species to the nuclei of interest such that the degree of polarization is increased well beyond what is allowed by the Boltzmann distribution. These procedures are referred to as "hyperpolarization methods" and may result in a dramatic >10^4-fold increase in signal strength over what can be achieved at thermal equilibrium.

For organic molecules, the two general methods of hyperpolarization are dynamic nuclear polarization (DNP) and parahydrogen induced polarization (PHIP). The greatly enhanced sensitivity obtained using these techniques can substantially reduce detection limits, thereby increasing the power of magnetic resonance to detect trace components. The greater signal-to-noise ratio (SNR) may also allow for rapid, sequential spectral acquisition and therefore is well suited for studying kinetics of many different chemical and biochemical processes.

Dynamic Nuclear Polarization (DNP)

DNP is a dissolution facilitated by the transfer of the polarization of unpaired electrons to the nuclei under study. Dissolution DNP methods require the sample be kept cold (e.g., <4 K) while irradiated by microwaves in a strong magnetic field (e.g., 3 T). After irradiation, the sample is rapidly dissolved using hot pressurized solvent and transferred to a NMR tube or an injection syringe for immediate NMR or MRI data acquisition. A free-radical doping agent (e.g., trityl radicals such as "OX63" and "Finland") must be present in the sample at mM concentrations during microwave irradiation in order to provide the needed nuclear polarization for intermolecular transfer. Generally, acceptable levels of polarization are achieved using irradiation times that are several tens of minutes to several hours in length.



^{13}C DNP spectrum of pyruvic acid (1-^{13}C). First scan of CIL's pyruvic acid (1-^{13}C) was provided by Karlos Moreno and Matthew Merritt from the UTSW Medical Center in Dallas, TX.

Parahydrogen Induced Polarization (PHIP)

PHIP transfers polarization directly from parahydrogen (para-H2) to nearby nuclei of interest or by using RF-based magnetization transfer methods. For organic molecules, para-H2 is either added directly across unsaturated carbon-carbon bonds or mixed with the sample under conditions such that polarization can transfer from para-H2 to sites within the molecule. Some advantages of PHIP over DNP are that a polarized sample may be attained quite quickly (on the order of seconds or minutes) and that free-radical doping agents are not required.

Metabolic Imaging

Perhaps the most exciting consequence of signal enhancement obtained using DNP and PHIP is the potential for *in vivo* ^{1}H, ^{13}C and ^{15}N monitoring of metabolism. In particular, ^{13}C magnetic resonance imaging (MRI) using hyperpolarized ^{13}C-enriched organic molecules offers significant advantages over ^{1}H-based imaging techniques, because background signals are not detected and the large chemical shift range for ^{13}C leads to increased molecular selectivity. Currently, there is is interest in the use of isotopically enriched hyperpolarized substrates for medical imaging because detailed, metabolic information (substrate localization and biochemical transformations) and physiological information (e.g., intracellular pH) may be obtained. In particular, there is great interest in the use of 1-^{13}C pyruvic acid as a dissolution DNP substrate to distinguish healthy from diseased tissue based on its conversion to lactic acid. Although the signal enhancement of hyperpolarized spin one-half nuclei decays with T_1, research is under way to establish long-lived nuclear states with the promise that metabolism may be studied over time scales of minutes or even hours instead of seconds.

Cover inset image courtesy of John Kurhanewicz

Enriched Substrates for Hyperpolarization

The following list of compounds has been employed in metabolic research as well as PHIP and DNP experiments. The presence of deuterium adjacent to the ^{13}C nucleus may aid in lengthening T_1 times due to eliminating ^{13}C-^{1}H dipolar relaxation. Studies have been done where one or more compounds are hyperpolarized in the same sample to probe multiple pathways concurrently.

Catalog No.	Description
CLM-1159	Acetic anhydride (1,1′-$^{13}C_2$, 99%)
NLM-3987-CA	Adenosine triphosphate (U-$^{15}N_5$, 96-98%)
CLM-116	L-Alanine (1-^{13}C, 99%)
CLM-1288	D-Arabinose (2-^{13}C, 98%)
CLM-3085	L-Ascorbic acid (1-^{13}C, 99%)
CLM-518	DL-Aspartic acid (4-^{13}C, 99%)
CDLM-4636	1,1-*bis*(Hydroxymethyl) cyclopropane (1-^{13}C, 99%; D_8, 99%)
CLM-548	Choline chloride (1,2-$^{13}C_2$, 99%)
NLM-8496	Choline chloride (^{15}N, 98%)
CLM-130	Ethanol (2-^{13}C, 99%) (<6% H_2O)
CLM-344	Ethanol (1-^{13}C, 99%) (<6% H_2O)
CLM-551	Ethanol (1,2-$^{13}C_2$, 99%) (<6% H_2O)
CLM-7350	Ethylpyruvate (1-^{13}C, 99%)
CLM-1527	D-Fructose (2-^{13}C, 99%)
CLM-4454	Fumaric acid (1,4-$^{13}C_2$, 99%)
CDLM-6062	Fumaric acid (1-^{13}C, 99%; 2,3-D_2, 98%)
CDLM-8473	Fumaric acid (1,4-$^{13}C_2$, 99%; 2,3-D_2, 98%)
CLM-3612	D-Glutamine (1-^{13}C, 99%)
NLM-1328	Glutamine ($^{15}N_2$, 98%)
CLM-420	D-Glucose (1-^{13}C, 98-99%)
CLM-746	D-Glucose (2-^{13}C, 99%)
CLM-504	D-Glucose (1,2-$^{13}C_2$, 99%)
CLM-2717	D-Glucose (1-^{13}C, 99%; 6-^{13}C, 97%+)
CDLM-3813	D-Glucose ($^{13}C_6$, 99%; D_7, 99%)
CLM-674	L-Glutamic acid (1-^{13}C, 99%)
CLM-1166	L-Glutamine (5-^{13}C, 99%)
CLM-1017	Glycine (1,2-$^{13}C_2$, 97-99%)
CLM-1510	Glycerol ($^{13}C_3$, 99%)
CLM-1397	Glycerol (2-^{13}C, 99%)
CLM-2093	α-Ketoisocaproic acid (1-^{13}C, 99%)
CLM-1189	D-Mannitol (1-^{13}C, 99%)
CLM-149	Oleic acid (1-^{13}C, 99%)
CLM-1889	Potassium palmitate (1-^{13}C, 99%)
CLM-8077	Pyruvic acid (1-^{13}C, 99%)
CLM-8849	Pyruvic acid 2-^{13}C, 99%)
CLM-9505	Pyruvic acid (1,2-$^{13}C_2$, 99%)
CLM-156	Sodium acetate (1-^{13}C, 99%)
CLM-381	Sodium acetate (2-^{13}C, 99%)
CLM-440	Sodium acetate (1,2-$^{13}C_2$, 99%)
CLM-441	Sodium bicarbonate (^{13}C, 99%)
CLM-1256	Sodium butyrate (1-^{13}C, 99%)
CLM-3706	Sodium D-3-hydroxybutyrate (2,4-$^{13}C_2$, 99%)
CLM-1577	Sodium L-lactate (1-^{13}C, 99%) 20% w/w in H_2O
CLM-1578	Sodium L-lactate (3-^{13}C, 98%) 20% w/w in H_2O
CLM-1082	Sodium pyruvate (1-^{13}C, 99%)
CLM-1580	Sodium pyruvate (2-^{13}C, 99%)
CLM-1575	Sodium pyruvate (3-^{13}C, 99%)
CLM-778	Tryptophan (1-^{13}C, 99%)
CLM-311	Urea (^{13}C, 99%)
NLM-233	Urea ($^{15}N_2$, 98%+)

"CIL's help was crucial in the molecular synthesis of the precursor of the first metabolic PHIP (parahydrogen induced polarization) reagent for real-time hyperpolarized imaging and spectroscopy."

– Dr. Pratip Bhattacharya
Department of Cancer Systems Imaging
The University of Texas MD Anderson Cancer Center

"The success of hyperpolarized ^{13}C MR studies relies heavily on having the appropriate stable isotope (^{13}C, ^{15}N, ^{2}H) labeled compounds to address the important biomedical questions being investigated. Only a decade after the first demonstration of dissolution-DNP hyperpolarized ^{13}C MR, metabolic imaging using HP [1-^{13}C] pyruvate was accomplished in prostate cancer patients. We have been using CIL labeled compounds for preclinical studies, and are looking forward to using their cGMP-labeled compounds for future patient studies. We have greatly appreciated CIL's interest and investment in this growing new molecular imaging technique, their friendly customer service, competitive pricing and excellent quality control."

– John Kurhanewicz
Professor of Radiology and Biomedical Imaging, Urology and Pharmaceutical Chemistry
Director of the UCSF Body Imaging RIG and Biomedical NMR Lab
University of California San Francisco

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- Unsurpassed synthetic organic experience using ^{13}C, ^{15}N and deuterium
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Gases for Hyperpolarization

^{3}He and ^{129}Xe are hyperpolarized using optical pumping methods. These materials are used in MRI to visualize airflow spaces and obstructions in the lung. The development of a new class of biosensers that comprise encapsulated ^{129}Xe is also an area of active research.

Catalog No.	Description
HELM-39	Helium (^{3}He, 99.95+%)
XELM-430	Xenon (^{129}Xe, 99%)

Deuterated Solvents for DNP

For DNP experiments, the use of deuterated solvents during and after microwave irradiation helps reduce nuclear relaxation rates, thus extending the time of which ^{13}C nuclei and other nuclei are hyperpolarized. All solvents used during polarization must form a "glass" at cryogenic temperatures to ensure the free radical is homogeneously dispersed within the solid sample.

Catalog No.	Description
DLM-4	Deuterium oxide (D_2, 99.9%)
DLM-10	Dimethyl sulfoxide (D_6, 99.9%)
DLM-16	Ethanol (D_6, 99%)
DLM-1229	Glycerol (D_5, 99%)
DLM-24	Methanol (D_4, 99.8%)

^{13}C-Depleted Deuterated Solvents

DNP experiments acquired at low temperatures in the solid state benefit from continuous-wave microwave irradiation so that unmodified solid-state NMR experiments (e.g., CPMAS 2D experiments) can be performed.The use of ^{13}C-depleted deuterated solvents will substantially reduce or eliminate unwanted ^{13}C signals from the solvent, thereby improving the quality of the obtained spectra.

Catalog No.	Description
CDLM-8660	Glycerol ($^{12}C_3$, 99.95%; D_8, 98%)
CDLM-3321	Dimethyl sulfoxide ($^{12}C_2$, 99.95%; D_8, 98%)

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